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C1  
b) determining the binding of said R0101 protein and said PCNA protein.

19 14. A method according to Claim 13, wherein said R0101 protein and said PCNA protein are combined first.

20 15. A method according to Claim 10 or 11, further comprising determining the activity of said R0101 protein in the presence of said candidate bioactive agent.--

### REMARKS

Applicants acknowledge the Examiner's objections to the Response and Amendment filed 1 June 2001, deemed non-responsive. Applicants hereby submit a replacement Amendment and Response without prejudice, disclaimer or admission.

Claim 1 has been canceled without prejudice, disclaimer or admission. Claims 10-15 have been added and consideration of these new claims is respectfully requested. Favorable consideration of the following remarks as they pertain to the new claims is requested.

Attached hereto is a marked-up version of the changes made to the instant application by the current Amendment. The attached page is captioned "Version with Markings to Show Changes Made."

Applicants point out that Claims 10 and 11, and dependent Claims 12-15 are drawn to the subject matter elected for prosecution in the present application. Particularly, the new claims are directed to the subject matter of inventive Group I, a method for screening for bioactive agents capable of binding to the cell cycle protein R0101. This election was made in the Response submitted by Applicants on 9 June 2000 and was acknowledged in the Office Action mailed 1 December, 2000 (paper no. 12).

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#### Information Disclosure Statement

Regarding the Examiner's remarks in paper no. 12 concerning the requirement for an information disclosure statement (IDS), Applicants respectfully point out that an information disclosure statement including form PTO-1449 listing 6 references was filed with the PTO on 16 August 2000 and was received by the PTO on 21 August 2000. Copies of the information disclosure statement and postcard are attached. If the Examiner has not received the listed references, Applicants will forward additional copies of the references upon request.

#### Drawings

Applicants acknowledge that correction of drawings is required in the present application. Applicants are in the process of preparing formal drawings and will submit such drawings in response to receipt of a Notice of Allowance.

#### Claim Rejections

##### Rejections Under 35 USC § 101

Claim 1 stands rejected under 35 USC § 101 as being drawn to subject matter with no apparent or disclosed specific and substantial credible utility. Applicants respectfully traverse.

The Office Action (paper no.12) expresses that the specification fails to demonstrate involvement of R0101 (p15PAF) protein in a particular physiological process that an artisan would wish to manipulate. The Action further expresses that there is an absence of knowledge as to the natural ligands of R0101 and as a result there is no patentable use for it. Applicants disagree and point out that the instant application discloses R0101 cell cycle

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protein binds to PCNA and modulates the binding of p21 to PCNA. These R0101 cell cycle protein activities, discussed below, support that R0101 has well-established utility.

### *Background of the Invention*

#### *PCNA is Involved in the Regulation of DNA Synthesis and Cell Cycle Progression*

PCNA plays an essential role in DNA synthesis, at least in part due to its function as a processivity factor for DNA polymerases delta and epsilon (see Kelman, *Oncogene* 14:629-640, 1997, a copy of which is enclosed as Exhibit A). Forced expression of PCNA anti-sense RNA in proliferating cells suppresses DNA replication and cell cycle progression (Jaskulski et al., *Science*, 240:1544-1546, 1988, a copy enclosed as Exhibit C).

#### *p21 Binds PCNA and Coordinately Regulates DNA Synthesis and Proliferation*

p21 is an inhibitor of cell cycle progression which coordinately regulates DNA synthesis and kinase activities underlying cell cycle progression. The interaction of p21 (through the C-terminus) with PCNA inhibits DNA synthesis, while the interaction of p21 (through the N-terminus) with cdk-cyclins inhibits their kinase activity and advancement of the cell cycle (Kelman, *supra*).

In addition, the p21 gene is directly regulated by the wild-type p53 proto-oncogene and is able to suppress tumor cell growth in culture (El-Deiry et al., *Cell* 75:817-825, 1993, a copy of which is attached as Exhibit B). This suggests that p21 is one of the major downstream effectors in the p53 pathway which appears to be dysregulated in a large number of cancers.

#### *Review of the Invention: Cell Cycle Protein R0101 Binds to PCNA and Competes with p21 for Binding to PCNA*

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The instant specification clearly establishes that R0101 possesses a conserved PCNA-binding motif, as outlined in Figure 2. In addition, the instant specification establishes that R0101 can bind to the nuclear proteins PCNA, cdk2, and cdk3 in a yeast two hybrid assay. Moreover, the instant specification establishes the functionality of the R0101 PCNA-binding motif by showing that a variant of R0101 with a sequence alteration in the conserved PCNA-binding motif does not bind to PCNA. Further, the specification clearly establishes that R0101 is localized to the nucleus where PCNA and p21 are found, as shown in Figure 4.

The binding of PCNA to p21 and the physiological relevance thereof were well known in the art at the time the present application was filed (e.g. see Kelman *supra*). The instant specification establishes (for example at figure 6) that R0101 can modulate the binding of p21 to PCNA, and that p21 can modulate the binding of R0101 to PCNA. Thus, the present specification describes a physiologically important R0101 ligand, particularly PCNA, and further describes the ability of R0101 to modulate a physiologically important interaction between p21 and PCNA.

#### *Review of the Utility Guidelines*

Applicants respectfully refer to the revised version of the guidelines to be used by Office personnel in their review of patent applications for compliance with the utility requirement of 35 U.S.C. §101, published in the Federal Register Vol. 66, No. 4, Friday January 5, 2001. Section B, paragraph 1, subparagraph c states:

If at any time during the examination, it becomes readily apparent that the claimed invention has a well-established utility, do not impose a rejection based on lack of utility. An invention has a well-established utility (1) if a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (2) the utility is specific, substantial and credible.

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*R0101 and Methods for Screening for Bioactive Agents Capable of Binding Thereto Have Well-Established Utility*

In view of the instant disclosure that R0101 binds to PCNA and modulates the binding of p21 to PCNA, Applicants submit that R0101 and methods for screening for bioactive agents that bind thereto have well-established utility.

PCNA is involved in the regulation of DNA synthesis and cell cycle progression. In addition, p21 binding to PCNA is involved in the regulation of DNA synthesis and cell cycle progression. Cell proliferation and DNA synthesis are physiological processes that one of ordinary skill in the art would wish to manipulate, and compositions that bind to PCNA and/or modulate the binding of p21 to PCNA would be recognized by one of ordinary skill in the art as being useful.

Further, binding to PCNA and modulating p21 binding to PCNA are properties that are not shared by all proteins and support that R0101 cell cycle protein has specific and real-world utility. Moreover, the utilities of R0101 cell cycle protein and the screening methods of Claims 10 and 11 are credible utilities. The Office Action does not present evidence that R0101 cannot bind PCNA, or that R0101 cannot modulate the binding of PCNA to p21. Further, the Office Action does not provide evidence that PCNA is not involved in the regulation of DNA synthesis and cell cycle progression, that the interaction of PCNA and p21 is not involved in cell cycle control and DNA synthesis, and that the manipulation of DNA synthesis and cell proliferation is not desirable. Accordingly, Applicants submit that a *prima facie* showing for lack of utility has not been made.

Applicants submit that R0101 and methods for screening for bioactive agents that bind thereto have well-established utility and respectfully request withdrawal of the rejection and allowance of the new claims.

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Rejections Under 35 U.S.C. § 112, first paragraph - how to use

Claim 1 stands rejected under 35 U.S.C. § 112, first paragraph. The Office Action expresses that since a patentable utility for the invention is not set forth, the specification fails to teach one of reasonable skill in the art how to make and use the invention for an asserted patentable utility. Applicants respectfully traverse.

Applicants submit that the instant invention has well-established and fully disclosed utility for reasons set forth above. Applicants request consideration of the remarks offered above as they pertain to the rejection under 35 U.S.C. § 112, first paragraph, and respectfully request withdrawal of the rejection and allowance of the new claims.

Rejections Under 35 U.S.C. § 112, first paragraph - enablement

Claim 1 stands further rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement. Particularly, the Office Action expresses that a method of screening for a candidate agent which binds a cell cycle protein is not enabled. Applicants respectfully traverse.

Applicants point out that claim 1 has been cancelled, and that the new claims are not drawn to such a screening method. Particularly, Claim 10 is drawn to a method for screening for a bioactive agent capable of binding to a cell cycle protein R0101 comprising an amino acid sequence having at least about 95% identity to the amino acid sequence set forth in SEQ ID NO:2 and which binds to PCNA. In addition, Claim 11 is drawn to a method for screening for a bioactive agent capable of binding to a cell cycle protein R0101 comprising the amino acid sequence set forth in SEQ ID NO:2 and which binds to PCNA. Further, Claims 12-15 depend from independent Claims 10 and 11.

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Applicants submit that the newly submitted claims are fully enabled by the instant specification. Applicants respectfully request withdrawal of the rejection and allowance of the newly pending claims.

### CONCLUSION

Applicants submit that the application is now in form for allowance and early notification of such is requested. If there remain issues that the Examiner believes may be resolved by telephone, he/she is respectfully requested to contact the undersigned at (415) 781-1989.

Respectfully submitted,

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Dated: 10 September 2001

By 

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

~~1. A method for screening for a bioactive agent capable of binding to a cell cycle protein R0101, said method comprising:~~  
~~—— a) combining a cell cycle protein R0101 and a candidate bioactive agent; and~~  
~~—— b) determining the binding of said candidate bioactive agent to said cell cycle protein R0101.~~

10. A method for screening for a bioactive agent capable of binding to the cell cycle protein R0101, comprising:

—— a) combining said cell cycle protein R0101 and a candidate bioactive agent; and  
—— b) determining the binding of said candidate agent to said cell cycle protein R0101;  
wherein said cell cycle protein R0101 comprises an amino acid sequence having at least about 95% identity to the amino acid sequence set forth in SEQ ID NO:2 and wherein said cell cycle protein R0101 will bind to proliferating cell nuclear antigen (PCNA).

11. A method for screening for a bioactive agent capable of binding to the cell cycle protein R0101, comprising:

—— a) combining said cell cycle protein R0101 and a candidate bioactive agent; and  
—— b) determining the binding of said candidate agent to said cell cycle protein R0101;  
wherein said cell cycle protein R0101 comprises the amino acid sequence set forth in SEQ ID NO:2 and wherein said cell cycle protein R0101 will bind to PCNA.

12. A method according to claim 10 or 11, wherein a library of candidate bioactive agents is added to a plurality of cells comprising a recombinant nucleic acid encoding said R0101 protein.

13. A method according to claim 10 or 11, further comprising:

—— a) combining a proliferating cell nuclear antigen (PCNA) protein with said R0101 protein and said candidate bioactive agent; and



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b) determining the binding of said R0101 protein and said PCNA protein.

14. A method according to Claim 13, wherein said R0101 protein and said PCNA protein are combined first.

15. A method according to Claim 10 or 11, further comprising determining the activity of said R0101 protein in the presence of said candidate bioactive agent.